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VASCULAR PROSTHESES WORKSHOP

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INTRODUCTION

The Vascular Prostheses Workshop opened with introductory remarks from Dr. Kaiser (chairman) and Dr. Packard (director, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute) regarding the role of workshops in identifying underdeveloped research areas and they described the process by which the National Heart, Lung, and Blood Institute (NHLBI) can strengthen research in these areas. The specific recommendations of this workshop will be considered by the Cardiology Advisory Committee for inclusion in the implementation plan of the NHLBI. Dr. Packard discussed the mandate of the Institute and the specific national plan areas. NHLBI supports major efforts in research and therapy for coronary heart disease and is also chartered to support research related to peripheral vascular disease. The results of the workshop should be of interest to research scientists in both areas.

OVERVIEW

Dr. Callow opened the scientific presentations by presenting an overview of the status of vascular grafts. He summarized the patency rates for various types of grafts in various anatomical locations and related this to clinical status.

Data from a number of sources were presented which showed that reversed saphenous vein grafts appear to have better patency rates than any of the commercially available tissue or synthetic grafts, and that even for the reversed saphenous vein graft, long-term patency diminishes as the anatomical location becomes more distal and runoff decreases.

It was noted that there is little experience beyond 3 years with any of the synthetic or tissue grafts, thereby making estimates of long-term patency difficult. In some instances, 5-year patency may depend upon reoperation within several years of implantation to remove clot or neointima; therefore some caution may be advisable when the surgeon discusses anticipated outcomes with the patient at the time of the initial operation.

The presentation stressed the need for common reporting practices in publishing clinical results so that data from individual centers could be evaluated in a meaningful manner. There was particular emphasis on the need for using the cumulative life table analysis method to report data, to report the reason for surgery (claudication, rest pain, ischemia), complicating factors (e.g., diabetes), angiographic documentation of runoff, and description of graft location. In addition, standardized procedures for retrieving and evaluating implants was deemed desirable and the formation of a national graft registry was suggested.

BASIC SCIENCE: BLOOD

Dr. Sauvage made several brief observations in opening the basic sciences session. He emphasized the need to understand the biological response to the types of grafts which might be implanted and noted that it is not possible to force a graft to successfully fulfill its function; rather, a successful graft will be the one which works in concert with the biological response.

At least three general approaches have been utilized in vascular graft development, including those for small vessels. These are 1) porous grafts which are preclotted and therefore present fibrin as the flow surface; 2) microporous grafts which do not require preclotting; and 3) grafts of impervious material of biologic or synthetic origin.

One important point which was raised at this time, and which was well recognized by program participants (although it was not formally discussed), is the role of the surgeon in determining the success of an implantation procedure. It was deemed desirable that the surgeon understand the role he or she may play in altering surface chemistry, fluid dynamics and vascular wall physiology by the choice of preimplantation procedures (preclotting, saline washes), positioning (angle of anastamosis), suturing techniques, graft size, and pharmacologic intervention.

Blood Material Interactions (Dr. Salzman)

The intact endothelium is a tissue which does not actively promote blood coagulation or thrombosis unless it is damaged. Additionally, the endothelial cell possesses enzymatic activities and produces agents which actually diminish or inhibit platelet aggregation (ADPase and PGI_2) and lead to the dissolution of the fibrin coagulum (plasminogen activator).

The normal host has a variety of delicately balanced means to maintain blood in a fluid state. The endothelium utilizes a variety of functions to inhibit coagulation and block platelet aggregation, as well as actively interfering with these processes once they have started. The blood itself contains a number of anticoagulants and under normal

flow situations, rheologically related thrombotic events are unlikely to occur. Finally, the tissues, particularly the reticuloendothelial system, continually remove circulating blood components, such as activated clotting factors, which have been damaged. A vascular graft alters this delicate balance, particularly since it may activate the coagulation and thrombotic systems and because it does not contribute any endothelial inhibitory functions in a given vascular segment.

Clinical trials to utilize systemic pharmacologic agents to balance the effects of such nonendothelialized areas have been disappointing, particularly the combination of aspirin and indomethacin. This may be because these drugs block aggregation but cannot prevent adhesion to surfaces; this adhesion by itself causes platelet damage and may alter fluid dynamics enough to compromise the device. Drugs such as PGI_2 which elevate platelet cyclic AMP have more promise than the nonsteroidal anti-inflammatory agents which function by blocking thromboxane production. PGI_2 blocks platelet aggregation at the surface of extracorporeal circuits and in increasing doses even blocks adhesion.

The need for understanding the histology of the graft surface in relation to platelet function was discussed. In baboons, platelet survival correlates with endothelialization of a vascular surface. It should be noted that in baboons, in contrast to man and dogs, the vascular graft surface does support endothelial cells. However, a return to normal platelet survival may occur even though the surface is not covered by endothelial cells. This is evidence that graft surfaces may become passivated by other unknown mechanisms. It has been noted in dogs that platelet survival and platelet serotonin content are abnormal for about 1 year after graft implantation, but eventually return to normal. Vascular grafts in dogs, and in humans, do not normally heal with complete endothelial surfaces. Thus, a passivating process unrelated to endothelialization must be occurring. While *in vitro* experiments identify some short-term passivating effects by albumin and by adsorption of antithrombin III on heparinized materials, the nature of the gradual *in vivo* passivation ("healing") is not known.

Dr. Salzman identified the approaches which might be made in vascular graft development and then presented results from his group of collaborators which related to these approaches.

One approach is to design thromboresistant materials. These may be thromboresistant either because they are bland and do not activate coagulation or thrombosis, or because they incorporate pharmacologic agents which will inhibit these processes when they are activated. The alternate approach to designing thromboresistant materials is to utilize pharmacologic agents to inhibit the coagulation and/or thrombotic process.

Platelet retention on bead columns was the method which was used to assay the thrombotic nature of several types of surfaces. In this type of experiment, it can be demonstrated that platelets are less reactive with polystyrene beads coated with albumin, and are more reactive with those coated with fibrinogen. The passivating nature of albumin and the thrombogenic nature of fibrinogen are poorly understood and should be regarded as research gap areas. For a series of polyalkylmethacrylates, it was found that hydrophobic surfaces were more thrombogenic, perhaps because plasma proteins are being adsorbed irreversibly. In a similar study with polyether urethanes, the length of the soft segment was varied. As length of soft segment increased, water adsorption also increased and appeared to be inversely correlated with platelet retention.

Fluid Dynamics (Dr. Karino)

Careful documentation of steady flow patterns in model systems and in natural arteries and veins has identified the junction geometries, flow rates, and volume ratios where turbulence, vortices, and laminar flow might be found. These studies have identified regions where secondary vortices may exist in nonpulsatile conditions (for example, in a venous pocket or at the site of a total occlusion). Formation of vortices in these model systems can be demonstrated to be due to flow that is not proportional to the cross-sectional area of the tubing. Pulsatile flow and compliant walls may alter some of these parameters and possibly produce more favorable conditions than in a rigid tube model with steady flow. However, studies of flow dividers, angles, and cross-sectional area ratios clearly demonstrate that surgical techniques and placement markedly affect the flow patterns in the main and side vessels.

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BASIC SCIENCE: MATERIALS

Compliance (Dr. Abbott)

Dr. Abbott began his discussion by defining the functions of a medium size artery with particular regard to its compliant properties. The artery serves as a conduit for blood, smooths the pulsewave, transmits pulstile energy, and matches the impedance of the periphery. The concept of impedance was discussed as a function of fluid resistance, compliance, and fluid inertness; examples of closed (large diameter to small diameter) and open (small diameter to large diamter) impedance mismatches were presented. The remainder of the presentation focused on the relationship of compliance, as an impedance component, to the patency of vascular grafts.

Compliance was defined as the percentage change of diameter with a change in pressure:

$$C = \frac{\Delta D}{D\Delta P} \times 100 .$$

The effect of compliance on flow in a pulsatile system was illustrated simply. If a system is rigid, flow is proportional to pressure; thus in diastole, flow would be diminished relative to systole. In a compliant system, on the other hand, as the pressure producing flow increases, a portion of the energy expands the compliant chamber in addition to producing flow; as pressure drops in diastole, the distended compliant chamber returns to its resting dimension with forward flow of fluid in a valved system. The hypothesis which is based on this concept is that in a system with reduced compliance and reduced flow during diastole, the residence time of blood components in the noncompliant segment will be increased, thereby increasing the probability of thrombosis and its sequelae (including intimal hyperproliferation and atherosclerosis).

The hypothesis has been evaluated using clinical data from humans and in animal experiments. Compliance of graft segments or vascular tissue was measured in vitro and in vivo. Patency rates of graft materials appeared to be directly correlated to their compliance. In dog experiments, it was shown that the compliance of synthetic graft materials decreases in less than 3 months implantation,

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while autologous tissue retained its compliance. To eliminate the effects of chemistry on graft patency, fiberglass mesh was wrapped around autologous cephalic veins and implanted in the femoral artery. Healing appeared to be similar in the wrapped vein and in the control vein graft. No difference in mural thrombus was observed; however, if the endothelial cells were damaged before implantation, the rigid grafts displayed more thrombus.

Deposition of Indium-111 labeled platelets onto vascular grafts was also assessed in the dog. At a given flow rate each graft material could be uniquely characterized by the rate and amount of deposition, as well as decline to a plateau level. It was observed in these studies that platelets deposit on the grafts at the site of open impedance mismatch.

Dr. Abbott concluded his presentation by noting that in light of conflicting reports, the role of compliance in acute, intermediate and long-term thrombogenicity remains to be clarified. If compliance does affect graft patency, the mechanisms by which noncompliant materials induce failure must be determined, and distinguished from effects of blood-material interactions and effects of porosity and roughness.

Suture Line Stresses (Drs. Marble and Kinley)

Dr. Marble continued the discussion of the effect of engineering properties of vascular prostheses and sutures on the host vessel wall. Data on the compliance of human tissues (childhood to old age) were presented and contrasted to measured values of compliance of vascular grafts. Even the least compliant human vascular tissue was more compliant than currently used vascular grafts. These data were used to describe the effect of compliance mismatch on the vessel wall.

It was shown that for an end-to-end anastamosis axial stress is at a minimum at the suture line; however, longitudinal shear stress is greatest at the suture line. This shear stress could be minimized at normal vascular pressures by using a graft to vessel diameter ratio of 1.4.

For an end-to-side anastamosis, force at the suture line increases with angle and with cross-sectional ratio. Forces as great as 10^8 to 10^9 dynes/cm^2 can develop in

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extreme situations; this exceeds the yield strength of the vessel wall (4×10^7 dynes/cm^2) and approaches that of the graft (0.3 to 2.2×10^9 dynes/cm^2) and suture (4 to 5×10^9 dynes/cm^2) materials. Suture line forces are best distributed by a continuous mattress suture, with maximization of graft to tissue contact. For end-to-side anastomoses, forces are best reduced by utilizing as small an angle as possible and by using a graft of the same diameter as host vessel. If a graft were available with the same compliance as the host vessel, suture line stresses would be minimized.

Surface Chemistry (Dr. Baier)

Expanded polytetrafluoroethylene (PTFE) grafts have become increasingly popular for clinical use. The low energy of these surfaces approaches that of what has been postulated to be the ideal for a nonthrombotic polymer.

There is only limited information regarding the relationship of surface free energy to in vivo performance when bulk chemistry is unchanged. However, recent data from implants retrieved from humans suggest that there is a certain range which is more blood-compatible. The critical surface tension of normal vascular tissue is about 25 dynes/cm. The surface free energy of PTFE is similar, as is the surface of most glutaraldehyde treated vein grafts. It can be demonstrated that although vascular prostheses which have remained patent after many months of implantation do not have endothelial or cellular surfaces, they do exhibit a critical surface tension of about 25 dynes/cm. On the other hand, graft materials with higher surface tensions (35 dynes/cm) will thrombose when implanted. None of the currently available grafts becomes truly endothelialized in humans; thus, the thrombogenic/nonthrombogenic properties of the graft are totally dependent upon the nature of the initial graft material and its eventual state after implantation.

Surface energy of the graft material might play a role in directing fibroblast penetration and proliferation in the adventitial matrix. The role of the fibroblast capsule in the success of an implantation is not clear. Modifications of the surface chemistry of the adventitial side of graft materials may be desirable to limit fibroblast proliferation which may unnecessarily mechanically stress the anastamotic junction.

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Porosity (Dr. White)

The porosity of a vascular graft affects patency and long-term healing. Numerous studies have shown that grafts with pore sizes between 100 and 300 um diameter will occlude within a few hours. In grafts with smaller pore sizes (down to 4 um), the amount of cellular ingrowth appears to be proportional to the pore size; grafts with pore sizes of 20 to 45 um appear to be optimal for patency. If surface chemistry is constant, graft porosity appears to determine which cell type populates the interstices, and thereby determine the eventual compliance of a graft material. Haratzka and Wright have shown that grafts with 20 to 45 um pore sizes are populated with fibroblasts and histiocytes; these grafts retain compliance. In grafts with pore sizes greater than 45 um, fibroblasts and collagen are primarily observed. The collagen tends to strangulate the graft and decrease compliance. In those areas of a large pore graft where small interstices are found, histiocytes may be found as well, but the larger spaces are filled with fibroblasts.

Grafts with the same pore size but constructed of different biomaterials have different healing characteristics. It can be shown that polymer chemistry may determine infiltration rate, cell type, and, therefore, compliance during the healing process. If the graft material stimulates a fibrohistiocytic response, the graft retains compliance better than a material which promotes fibrous ingrowth with related abundant collagen production. It has been observed that Biomer grafts promote rapid cell ingrowth and become less compliant after 1 month; silastic grafts prepared in the same manner show slower cellular ingrowth and retain their compliance. Both grafts were 20 to 30 um pore size; fibrohistiocytic tissue was found in both, as well as type I and type III collagen. However, the balance of collagen production, maturation, and degradation is presumed to be different in the two grafts, thereby affecting compliance.

The anatomic position of a graft may require a given porosity for a particular benefit. While rapid cellular ingrowth leads to loss of compliance, it also minimizes chances of infection. This property is highly desirable in certain situations. Pore sizes and polymer chemistry which promote fibrohistiocytic growth (granulation tissue) are probably preferable for small vessel prostheses. The mixed cell population may modulate collagen production and preserve graft compliance.

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Cellular Linings (Dr. Herring)

Large diameter Dacron vascular grafts which incorporate endothelial cells into the clot at time of implantation (one stage technique) remain patent and develop a completely endothelialized surface within a period of several weeks in dogs; grafts which are clotted in the usual manner never develop this endothelial surface in dogs or humans.

For smaller vessels, several techniques were evaluated when it was determined that the one stage procedure was unsuccessful in this application. Dacron and expanded Teflon (e-PTFE) 4 mm grafts were exposed to whole blood and jugular vein endothelial cells and cultured for 1 week before implantation. Endothelial cells are found throughout the interstices at this time. Under all conditions studied, Dacron grafts occluded, perhaps due to the irregular surface topology of the graft with incomplete endothelialization. Although red thrombus was observed on cultured e-PTFE grafts at 1 hour postimplantation (1 cm grafts) the grafts remained patent and then healed with an endothelialized lumen within 1 month (6 cm). Untreated e-PTFE grafts were always occluded under these conditions. Thus, endothelial cells precultured on the surface were unable to prevent clot formation at time of surgery, but may have promoted the healing process.

During the course of these studies, it was discovered that for each graft diameter there is a maximum critical length beyond which the untreated graft will always thrombose. Dacron and e-PTFE grafts were identical in this respect. Grafts 3 mm in diameter will tend to remain patent only if the length is less than 4 mm; 4 mm diameter grafts will invariably thrombose if the length is greater than 40 mm. Therefore, any rigorous test of a new material or procedure for small vessel prostheses should include grafts which are longer than these critical lengths to demonstrate advantages over currently available materials.

It was concluded that for vascular graft evaluation, animal models should be chosen which do not rapidly cover the graft surface with endothelium and that the animal be large enough so that grafts longer than the maximum critical length can be evaluated.

Additional research in this particular area is necessary to determine whether there are any cellular changes using the tissue culture technique, to better define the role of the polymer substrate in directing the healing process, and to develop a better understanding of the factors which promote endothelial healing in some species but not others.

PATHOLOGY

Peripheral and Coronary Grafts (Drs. Szilagyi and Bourassa)

Information regarding pathological changes in vascular grafts in man has been obtained by the indirect technique of contrast angiography in relatively large numbers of patients and by direct morphological observations of specimens obtained at operation or autopsy in a much smaller number of patients. The need exists for the development of noninvasive techniques for the serial evaluation of vascular grafts. Potentially useful methods include radioisotopic imaging with agents such as platelets labeled with Indium-111, computed tomographic (CT) scanning, digital radiography and ultrasonic imaging. The need also exists for correlation of the angiographic and noninvasive imaging results with direct morphological observations in larger numbers of patients.

Available data were reviewed for prosthetic grafts and autogenous saphenous vein grafts implanted for peripheral vascular disease of the lower extremities and autogenous saphenous vein grafts used for treatment of coronary artery diseases. General similarities were noted for pathological changes in peripheral and coronary grafts. The need for appropriate procedures to excise, maintain, and implant autogenous veins in such a manner as to preserve endothelium was stressed, particularly for peripheral vascular grafts. Early graft failures were due to graft thrombosis and late graft failures to severe diffuse intimal fibrosis, atherosclerosis and/or repetitive layering of compacted fibrin. In peripheral vascular surgery, long-term results have been more favorable with bypass of large versus small arteries. The major predisposing factor for these changes in both the peripheral and coronary systems was identified as a low flow state related to poor distal runoff. To date, only limited information is available regarding the potential beneficial effects of various forms of anticoagulation and antiplatelet therapy for amelioriation of the pathological changes in vascular grafts.

Implant Retrieval (Dr. Anderson)

Much of the available information regarding mechanisms of graft failure has come from retrospective reviews by

individual investigators of their own material. A notable exception is the vascular graft registry and implant retrieval program of the Cleveland Vascular Society. This program provides for data collection in large numbers of cases (2,728 cases registered between 1978 and 1980) and also provides a much needed mechanism for graft retrieval. These grafts can be used not only for standard morphological studies but also for some advanced studies of graft biochemistry, blood-materials interactions and factors governing endothelialization.

Animal Models (Dr. DeWeese)

Despite the importance of clinicopathological studies in man, it is also clear that testing in animal models is essential for obtaining basic information for new and already available prostheses. The dog appears to be the most suitable animal species because of general similarities in the graft-host response in dog and man. Implantation of prostheses in the aorta serves as a model of large vessel grafting whereas implantation of prostheses in the carotid, femoral and coronary beds are used for modeling small vessel grafting. Further work is needed to standardize procedures and protocols in the dog, as well as to explore the potential utility of primate and small animal models. The importance of long-term testing of grafts in animal models was stressed. Animal tests should be continued for sufficient length of time for intimal proliferation to be observed.

CLINICAL EVALUATION

This final set of three papers emphasized the need for a common language to facilitate comparison of results and highlighted the multifactorial situation which will exist when trying to assess the properties and clinical performance of one graft versus another.

Clinical Trial Design (Dr. Bernhard)

The process by which three vascular surgery centers agreed to undertake a clinical trial was outlined and the data reporting forms with attendant definitions were described. Among the areas where agreement was required were: 1) methods to describe preoperative condition, including hemodynamics and arteriography; 2) surgical procedures, including vein harvesting procedures, method of suturing and anticoagulation, and use of intraoperative arteriography; 3) postoperative care and followup, including prophylactic use of aspirin and presantin, and quarterly diagnostic evaluation (pulses, ankle pressures and selected arteriography). The trial is now under way and patients are being entered. Patients with adequate saphenous veins are randomized into the control group and the trial group; patients with inadequate saphenous veins receive the synthetic graft, are evaluated by the same procedures, but analyzed as a separate group. A number of additional variables was elucidated (including clinical indications, graft position, arterial runoff, and new or repeat operation). These many variables emphasize the need for multicenter cooperation to achieve enough patients for statistical analysis.

Among the issues not readily foreseen or resolved in categorizing patients are sequential grafts, composite grafts, length of graft, site of proximal anastamosis, and extent of patient compliance with antiplatelet therapy.

The need for randomized clinical trials for evaluation of new prostheses was recognized. It was also conceded that this could be difficult to realize in a time of rapid development where new prostheses are appearing frequently attended by vigorous advertising campaigns. The agreement of several geographically separated surgical groups to standardize certain aspects of their clinical procedures was considered to be a major positive step.

Characterization Parameters (Dr. Mortensen)

The discussion of randomized trials illustrated the number of patient-related variables which must be considered when one type of graft is used; the parameters which should be characterized for each type of graft was discussed in the subsequent presentation. The physical factors and parameters of biocompatibility were listed and have been published in greater detail in a Food and Drug Administration (FDA) report. The need for objective evaluation of each of these parameters was emphasized. However, it was also recognized that the clinical meaning of some types of objective data has not yet been established. To establish the significant boundaries of objective, quantifiable tests, their relationship to clinical performance in humans must be established. This can be accomplished in part by careful evaluation of explanted prostheses and documentation of their modes of failure. This information, when related to objective test results, should lead to a well-defined procedure for testing prostheses under development. When the annual market for vascular grafts is considered (350,000 patients with grafts larger than 6 mm, 200,000 patients with smaller grafts) the desirability of comparable testing and evaluation methods becomes apparent.

Standards Development (Dr. Wright)

Voluntary groups of physicians and manufacturers are developing standards for testing and labeling vascular grafts. It is recognized that even the best graft will be subject to technical failure (such as kinks or twists introduced during surgery, or inappropriate anatomic placement). However, certain minimal standards of mechanical properties can now be established. At the moment, it is recognized that there is no ideal test which describes strength, thrombogenicity, and durability. Furthermore, there are no widely applied definitions of porosity, compliance or healing. Methods to encourage endothelial growth, to evaluate patency, and identify infection are currently underdeveloped areas.

RECOMMENDATIONS

It was the uniform opinion of the moderators, speakers, and participants that the development of a small vessel prosthesis for use in those anatomic positions requiring a vascular graft 4 mm or less in size should be the foremost goal in the area of vascular prostheses. It was the unanimous feeling of the workshop that if a prosthesis of this size could be developed dealing with all the problems of blood-material interactions, mechanical properties, physical chemistry, surface morphology, and fluid dynamics, then the graft material would be suitable for a larger size prosthesis as well. It is obvious that all of the problems related to an intravascular graft are accentuated in the small vessel prosthesis where the flow may be low and the vascular bed to be perfused is small.

Justification

There is ample critical evidence that at the present time no satisfactory small vessel prosthesis exists. The clinical data on peripheral arterial reconstruction using either natural or synthetic vascular grafts indicate only a 40-60 percent long-term patency rate at best. In the patient who has peripheral vascular disease, it might be advantageous to use a small vessel prosthesis and thereby save the autogenous saphenous vein for subsequent use for coronary bypass. In addition, coronary artery bypass patients with diseased saphenous veins or whose saphenous veins have already been used for peripheral or coronary bypass would benefit from an appropriate vascular prosthesis. In the pediatric age group, a satisfactory small vessel prosthesis could be used as a temporary shunt and might improve the late results of the conduit procedures because of the problem of obstruction due to intimal proliferation.

In summary, there is a large clinical need for the development of small vessel prostheses for use in peripheral vascular surgery, coronary artery surgery, and pediatric cardiac surgery.

Clinical Efforts

Although the ultimate value of any vascular prosthesis must be determined by comparison with other grafts in a prospective randomized trial, it is felt that there is not a need at this time for such a trial. As new prostheses are developed, the need for their evaluation by a prospective randomized trial should be considered. There is a randomized trial now ongoing supported by non-NIH funds to evaluate one type of synthetic vascular graft relative to saphenous vein; the progress and problems encountered of this effort at three independent institutions will be followed with interest by those who may initiate future trials, as well as by the vascular surgeons who are most anxious to learn the scientific results.

It may be that one method of collecting meaningful clinical data would be to establish a national registry for peripheral vascular surgery. Participating surgeons in such a registry would agree to indications for surgery, methods of diagnosis, types of procedures, the data required for evaluation and finally surgical followup. If such a registry were to be undertaken, it might use as a model the coronary artery surgery study now under way.

It was strongly recommended that the conclusions of the workshop be referred to the appropriate professional societies. It is hopeful that these societies help to develop the criteria for evaluation of prosthesis and the standards for vascular surgery. It was felt that the professional societies would be the appropriate groups to exert meaningful influence on the practices in vascular surgery.

Research Efforts

1. Develop a proper animal model to evaluate and test vascular prosthetic material and graft. This research should include evaluation of species differences and should elucidate the bases for these differences. In addition, animal models should be developed to study both the short- and long-term results. Long-term testing might require 3 to 5 years followup.

2. In the development of small vessel prostheses basic research is required in the following areas:

a) The healing process: modification and mechanisms

b) Pharmacologic and rheologic considerations

c) Evaluation of such things as a thrombotic velocity potential and evaluation of procedures to increase rate of flow into small distal vascular beds

d) Mechanical properties, the role of compliance, the anastomotic line and suture material

e) Physical chemistry

f) Surface morphology

g) Endothelial cell linings: methods of tissue culture, seeding of prostheses, and

h) Fluid dynamics.

All of these projects must be related to a time frame involving the host-graft and graft-host response to acute and long-term changes. The above research areas might well be those that could be stimulated by targeted research through the RFA or RFP mechanisms.

Summary

The workshop concensus is that the most pressing need at this time is funding for research in the development of an improved small vessel prosthesis. In the research area, the highest priorities should be given for the development of a satisfactory animal model for the evaluation of both short and long studies and specific basic research in the areas of the healing process and blood-material interactions, including the role of mechanical properties, physical chemistry, surface morphology and fluid dynamics.

Long-term goals might include the establishment of a national registry of results from peripheral vascular surgical procedures and a prospective randomized clinical trial of vascular prostheses. In the realm of preventive

medicine, methods to eliminate, alter, or delay arteriosclerotic changes in the vascular system should be supported. Lastly, the appropriate professional societies and agencies should be encouraged to establish criteria for the evaluation of prostheses and the development of standards of care.

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ABSTRACTS

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CURRENT STATUS OF VASCULAR GRAFTS

Allan D. Callow, M.D.

In the high flow, low resistance locations of the aorta, iliac and proximal femoral arteries, most currently used fabric prostheses are satisfactory. Complications of large diameter grafts are usually long-term and consist of angulation, dilatation, and fabric fatigue. For grafts below the inguinal ligament, both fabric and of animal origin, porosity, compliance, conformability, resistance to buckling and infection, and the blood graft interface are of increasing importance, and in the low flow, high resistance distal tibial location, may be critical. Patency rates to the tibial and peroneal arteries for all types of graft are diffcult to compare because of lack of a standard method of reporting and experience beyond 3 years is meager. The "ideal" vascular prosthesis of 5 mm or less is not yet available and some of the newer grafts may have been applied clinically prematurely.

Future Research Opportunities

Man fails to develop a tissue-lined endothelialized graft and at the Tufts New England Medical Center our research efforts have been directed to a study of those phenomena which may enhance or inhibit endothelialization, and early thrombus formation. Utilizing ^{111}Indium and the autologous baboon platelet, Dacron grafts consistently bind more platelet associated activity than PTFE and autografts. Maximum platelet associated activity occurs up to 60 to 120 minutes following implantation of the graft with no further increased activity through 48 hours. Concurrent studies on vascular endothelial cell tissue culture seeding and innoculation and factors influencing fibrinogen fibrin conversion are under way. Additional research should be directed to optimal filament size, shape and density of the graft for tissue ingrowth, and factors which influence the thrombogenicity of the flow surface. Endothelial cell seeding, fiber coating with a negatively charged hydrogel and anticoagulant-antiplatelet agents are in need of investigation. Other areas worthy of study include methods of prevention and early detection of graft infection, standardized uniform methods of accelerated testing of grafts, a national vascular registry, and a randomized prospective controlled refereed study of newer graft material.

BLOOD-MATERIAL INTERACTIONS

Edwin W. Salzman, M.D.

The resistance to thrombosis of normal endothelium is a product of many factors: chemical and biological blandness and failure to activate platelets or the intrinsic clotting system; active inhibition of thrombotic events (e.g., ADPase activity, generation of prostacyclin, secretion of plasminogen activator); capacity for regeneration and healing; optimized hemodynamics with streamlined flow, avoidance of flow separation, vortices or recirculating eddies; natural inhibitors of coagulation in the blood; and tissue clearance of activated hemostatic elements. Among vascular grafts, only transplanted living vessels can exhibit all of these features, and even they suffer from the initial trauma of implantation and the deprivation of their vasa vasora and from late degenerative changes to which they are no less susceptible than is the host vessel. Virtually all nonnatural surfaces activate factor XII or allow platelet adhesion and subsequent secretion of biologically active platelet contents and aggregation, or both. In addition, all prosthetic grafts have a junction with the living vessel, which is subject to excoriation of endothelium and thrombosis independent of the thromboresistant properties of the prosthesis itself. Several approaches have been addressed to these problems: bland surfaces have been developed, exhibiting an optimized balance of hydrophobicity and hydrophilicity, a lack of crystallinity a minimal capacity for hydrogen bonding and electrostatic interactions, and perhaps the absence of a regular repeating structure; actively antithrombogenic surfaces have been prepared by bonding biologically active agents such as heparin to the surface; materials have been produced whose initial interactions with blood elements are limited to the laying down of a "controlled" layer of thrombus, which subsequently presents to the blood a compatible film of natural biological substances. All of the above are imperfect, so reliance has been placed as well on ancilary pharmacologic measures, including anticoagulants or drugs that inhibit platelet activation by increasing platelet cyclic AMP, reducing the platelet production of prostaglandin endoperoxides and thromboxane A_2, increasing the vascular production of prostacyclin, or by other less well-defined mechanisms.

FLUID DYNAMICS IN NATURAL VESSELS

Takeshi Karino, Ph.D.

Fluid mechanical factors are suspected to play an important role in the localization of platelet deposition on the vessel wall in the circulation as well as in vitro circulatory devices. I have previously shown that the annular vortex formed downstream of a model axisymmetric stenosis provides favorable conditions for the genesis, growth and trapping of platelet aggregates as well as the enhanced adhesion of cells onto the vessel wall. To relate these findings to blood flow in vivo, a series of flow studies has been carried out using transparent arteries and veins of various geometry prepared from postmortem humans and dogs.

(i) Arterial branches. In dog abdominal aortas containing branches of celiac, cranial-mesenteric and renal arteries, paired vortices symmetrical about the common median plane of the aorta and branches were formed downstream of the junctions. It was striking that the corners at the flow dividers were sharp with a sudden decrease in aortic diameter distal to the junctions, while the opposite corners were gently rounded. Thus, under physiological flow conditions there were no vortices in the branches and those in the aorta were small and confined to thin layers close to the vessel wall surrounding the mainstream. Compared to our previous results in model T-junctions with sharp corners, the geometry of the aortic branches appear to be optimal for minimizing vortex formation. Paired vortices were also observed in the sinus of a human internal-external carotid artery bifurcation.

(ii) Venous valves. In a 2 mm diameter dog saphenous vein containing a two-leaflet valve, paired vortices were formed in each valve pocket. Particles continually entered the pockets from the mainstream, describing spiral orbits of decreasing diameter before rejoining the mainstream. A truly stagnant region existed in the deepest portion of each pocket where a secondary vortex was located. Here, at very low shear rates, red cell aggregates were formed which sometimes adhered to the vessel wall, an event which supports the hypothesis that venous thrombi originate in valve pockets.

Studies are being extended to flow in the aortic arch, the circle of Willis and the coronary arteries.

Future Research Opportunities

It appears that the geometry of vessel branches in the circulation is designed to minimize flow disturbances which result in extra energy loss and damage to vessel wall as well as to blood cells. Hence, it is desirable to study the three-dimensional arrangement of real arteries and veins so that vascular prostheses may be modeled as closely as possible to living vessels.

COMPLIANCE OF VASCULAR GRAFTS

William M. Abbott, M.D., Kevin C. Hanel, M.D.

The role of viscoelasticity in pulsatile arterial flow was recognized over two centuries ago, yet its application to arterial graft design is a recent phenomena. A stiff graft in the arterial circulation theoretically interferes with the efficient transfer of pulsatile energy resulting in flow separation, turbulence, endothelial shear stress, and increased anastomotic stress. Consequences of these adverse forces include acute graft thrombosis and long-term sequelae, such as anastomotic disruption, false aneurysm, and intimal hyperplasia.

The contribution of a compliance mismatch to graft failure compared to the other determinants, such as blood flow, surface thrombogenicity, and blood coagulability is difficult to quantitate but has been the subject of ongoing research in our laboratory for the past 7 years. There have been a number of research clinical studies correlating graft patency and graft compliance demonstrating that those which are good match with the host artery are superior. We have demonstrated experimentally that vein grafts rendered incompliant have a propensity to thrombus development and recent work in our laboratory on platelet graft interactions using Indium-labeled platelets suggests that more platelets accumulate at the distal anastomosis where the effects of compliance mismatching seem most consequential. Lyman's group has also demonstrated that copolyurethane grafts, which are incompliant develop intimal hyperplasia at this site and fail more commonly than those that are compliant. We are presently studying the chronic effects of incompliance on endothelial morphology and subintimal proliferation in vein grafts. There are other centers engaged in developing compliant grafts from different elastomers and we are engaged in studying the thrombogenic and biophysical properties of these grafts in an effort to define their optimal requirements.

Much work needs to be done to further clarify the role of compliance in acute and chronic graft failure, the mechanism by which it exerts that role, and to develop technology to non-invasively study graft mechanical properties. Compliance may not be the major determinant of graft failure; however, it is important, as it is a manipulable part of the manufacturing process. Even if compliant grafts become stiffer with fibrous incorporation, initial compliance may decrease the short-term propensity to thrombosis and allow the grafts to develop a blood compatible surface.

SUTURE LINE STRESS IN VASCULAR ANASTOMOSES

C. Edwin Kinley, M.D., F.R.C.S.(C)
and Alan E. Marble, Ph.D., P. Eng.

For the past 12 years our group, as well as Baird et al. at Harvard, Hokanson's group in Seattle and Szlagyi's in Detroit, have been studying the compliance characteristics of natural and artificial arteries as well as the yield strengths of these arteries and of suture materials. Using these data, mathematical models of end-to-end and end-to-side anastomoses have been created in order to determine the effect of the significant compliance mismatch between host and synthetic arteries on stress at the anastomosis. For the end-to-end anastomosis, the axial stress acting on the suture material connecting the two dissimilar arteries has been estimated from the model to be in the order of 3×10^6 dynes/cm^2), but varies with the angle of the end-to-side geometry as well as with the cross-sectional area ratio between graft and host artery. The tensile yield strength of various suture materials have been measured in our lab and have been found to be an order of magnitude (10 times) larger than the stress which the suture is required to bear in both anastomotic configurations. However, we have found that the yield strength of the host artery is an order of magnitude less than the stress acting on the suture material. This suggests that in using noncompliant grafts, suture forces could cause the suture to tear through the host arterial wall unless sufficient sutures per cm, and maximum suture-host artery contact area is established. A more constructive recommendation would be to design a vascular prosthesis which has the same compliance as a host artery. Model predictions indicate that this would minimize anastomotic stress and reduce the possibility of suture line disruption.

SURFACE CHEMISTRY OF SMALL VESSEL PROSTHESES IN HUMANS

Robert E. Baier, Ph.D.

The blood-contacting flow surfaces of differing vascular conduits evoke considerably different responses in terms of plasma protein adsorption and denaturation, subsequent platelet attachment and alteration, and gross patency over the long term in humans. First, it should be recognized that even the autogenous natural blood vessels of first choice for vascular reconstruction are often seriously compromised at implantation by serious loss of endothelial integrity, thus presenting a subendothelial lamina as the actual blood-contact surface. Preserved, stabilized homografts, heterografts, and xenografts present similar, cell-denuded interfaces. Synthetic polymer grafts present strikingly different flow surfaces varying in both chemistry and texture.

Examination of pre- and postimplant specimens from human small vessel prostheses, using techniques of internal reflection infrared spectroscopy, surface energy analysis, and electron microscopy, has revealed the following:

Contrary to conventional axioms, expanded polytetrafluorethylene (Teflon) and textile polyethyleneterephthalate (Dacron) grafts do not support endothelial coverage over most of their surface areas even with long implant times. Rather, when they remain patent, it is the result of an equilibrium obtained between lytic and digestive mechanisms of the flowing stream and the continuing process of localized thrombogenesis and/or thromboembolism at the flow surface. Actual colonization of the pseudointimal face by ingrowing cells from the adventitial side of porous grafts is seldom observed. Further, expanded Teflon grafts are subject to significant lipid uptake in some cases, and porous Dacron grafts can eventually embrittle by calcification. Poorly cross-linked, enzyme-digested heterografts, although initially more thromboresistant, often fail by aneurysm. Even the well-stabilized, thromboresistant, compliant human umbilical cord vein prostheses introduced recently are subject to considerable lipid uptake in some hosts.

Future Research Opportunities

- Truly synthetic, compliant small vessel prostheses with internal surface chemistries similar to those of natural healthy blood vessels, or even deendothelialized blood vessels, remain to be developed. One important design criterion is that the empirically determined critical surface tension be close to 25 dynes/cm.

- Improved small vessel prostheses of biological origin, generated by tissue response to implanted synthetic, mesh-wrapped rods in animals, remain to be proven suitable by criteria of thromboresistance, immunoresistance and biodegradation resistance in human hosts.

POROSITY OF VASCULAR PROSTHESES

Rodney A. White, M.D.

Porosity is an essential component for long-term function of vascular prostheses. No material has been developed which will remain patent in a nonporous form. Theoretically, porosity is required for healing by providing a scaffold for ingrowth of peri-prosthetic tissues. Porosity may be required for transfer of fluid and ions in prostheses even if tissue ingrowth does not occur. Increased permeability of vascular grafts has been shown to enhance tissue incorporation. Wesolowski described an inverse relationship between porosity and calcification. Moore has shown that highly porous, rapidly incorporated grafts have less susceptibility to systemic infection.

Porous forms of Dacron and Teflon constitute the majority of currently implanted vascular prostheses. Fiber grafts are woven (macroporous), knitted (microporous) or fabricated as velours or felt to provide a fine porous pattern. Current polytetrafluoroethylene grafts have a node and fibril microporous configuration with fibril lengths of approximately 30 um.

The tissue ingrowth of porous grafts is related to pore size. Pore sizes < 10 um are not ingrown. Implants with pore sizes > 10 um but < 45 um become ingrown with fibrohistiocytic tissue and capillaries. Implants with pores > 45 um are ingrown with organized fibrous tissue and minimal histiocytic response. The phenomenon of differential ingrowth may have important functional significance. Prostheses which heal with organized fibrous tissue have the potential for long-term contracture, strangulation of vascularity and calcification. Fibrohistiocytic tissue has low mechanical strength and does not appear to contract or calcify. Elastomeric microporous vascular prostheses which are minimally ingrown or ingrown with fibrohistiocytic tissue maintain compliance with short-term implantation.

Future Research Opportunities

Future study is needed to determine the optimal porous configuration of various materials to provide the desired degree and nature of incorporation of vascular grafts. The need for ingrowth may be determined by the site of implantation. Aortic grafts may require well incorporated materials to provide stability and resistance to infection. Small internal diameter applications may require less well ingrown grafts to maintain compliance. Studies are needed which determine the independent effects of porous parameters on long-term function of vascular replacements.

ENDOTHELIAL LININGS
AN APPROACH TO SMALL ARTERY REPLACEMENT

Malcolm Herring, M.D. and John Glover, M.D.

Endothelium, unlike the known biomaterials, can control coagulation on the arterial flow surface, respond to changes in the flow surface environment and regenerate following injury. Therefore it is reasonable to hope that endothelial linings will bring success to small artery grafting. We developed a technique for seeding autogenous canine cells onto Dacron prostheses and implanting the prosthesis in a single-staged operation. This preparation proved unsatisfactory for small artery prostheses, presumably because the lining is incomplete at the time of implantation. To achieve confluence at implantation. Linings cultured on e-PTFE proved stable over a 1-month test interval. Still, surface coagulation was incompletely inhibited during the early minutes after implantation. A more troublesome problem is our inability to culture these linings consistently.

The direction of future research must include a well-defined laboratory model for implantation studies. The direction of biomaterials development should be changed from the goal of blood compatibility toward the goal of endothelium compatibility. Basic information should be accumulated regarding the changes in endothelium during harvesting and suspension procedures, the mechanism and kinetics governing the adhesion of the cells to their substrate, the qualities of substrate which promote cell adhesion and growth, and the differences in species of endothelium.

POSTOPERATIVE BEHAVIOR OF SOME ARTERIAL SUBSTITUTES IN FEMOROPOPLITEAL ARTERIAL GRAFTING

D. Emerick Szilagyi, M.D.

This report summarizes the author's histologic, roentgenologic, and clinical observations in cases with femoropopliteal (FP) arterial reconstruction utilizing his Dacron prosthesis and autogenous vein grafts.

After extensive experimental investigation of its biologic potential (Szilagyi et al., Surgery 55: 165, 1964), the woven seamless uncrimped Dacron prosthesis constructed of an elasticized (i.e., Helanca) yarn was introduced in 1957 and has since been employed in about 3,000 cases of occlusive and aneurysmal arterial disease in the aortoiliac (AI) and FP regions. In terms of both late cummulative patency rates and clinical improvement the results were excellent in the AI and poor in the FP operations (Szilagyi et al., Ann Surg 162:453, 1965). Postoperative roentgenologic and histologic evidence was obtained strongly suggesting that this variance was primarily the result of the differences in the hemodynamic factors of the two topographic regions operating in a histologic environment that was intrinsically thrombophilic.

The results of 597 femoropopliteal operations with autogenous vein grafts in patients with clinical characteristics closely similar to the features of those above (Szilagyi et al., Surgery 86:836, 1979) were satisfactory (cumulative patency rate 52.5 percent at 5 and 41.3 percent at 10 years po). Postoperative angiographic examinations and histologic studies of recovered graft specimens (Szilagyi et al., Ann Surg 178:232, 1973) disclosed, however, that morphologic changes of varying types and severity occur in about one-third of the cases; of these the most important ones were atherosclerosis and intimal thickening. The changes were progressive and, if uncorrected, often led to graft failure. These and collateral experimental observations showed that the technique of harvesting and the method of temporary storage of the vein graft importantly affected some of the postimplantation changes. Care in these maneuvers as well as close postoperative followup for early detection of changes promised to improve the performance of the grafts.

POSTOPERATIVE CHANGES IN SAPHENOUS VEIN AORTOCORONARY BYPASS GRAFTS EARLY AND LATE EVENTS AND THE EFFECTS OF INTERVENTIONS

Martial G. Bourassa, M.D.

Aorta-to-coronary saphenous vein graft patency rates, based on prospective sequential angiographic studies, ranged from 87 to 92 percent less than 1 month after surgery and from 74 to 85 percent approximately 1 year after surgery. The attrition rate of bypass grafts averaged 2.2 percent per year between the first and sixth year after surgery. Occlusion during the first month was due to thrombosis and occlusion at 1 year was caused by fibrous intimal proliferation of grafts. The most important determinant of graft patency at 1 year was the runoff capacity of the recipient coronary arteries. The quality of the surgical techniques rated second in importance. The type of recipient coronary arteries, degree of proximal obstruction, quality of wall motion, and type of bypass did not appear to influence graft patency. Late graft occlusion was related to atherosclerosis which became manifest only after a minimum of 2 years. Whether thrombosis and the formation of endothelial hyperplasia in grafts with poor runoff and low flow velocity can be prevented by the administration of anticoagulants or platelet inhibitors has not been clearly demonstrated. Likewise, the role of blood lipids in the development of graft atherosclerosis is controversial. A close correlation between hyperlipemia and atherosclerosis in the grafts has been reported. However, we have not been able to confirm such a correlation in our cases.

The usefulness of computed tomography, digital fluoroscopy and external pulsed Doppler echography in the sequential study of graft patency and function should be further evaluated. Using these noninvasive methods and/or angiography, large scale prospective studies should be undertaken to determine whether anticoagulants or platelet inhibitors will improve patency in grafts with a limited outflow capacity and whether better control of risk factors will reduce the incidence of late graft atherosclerotic occlusion or stenosis.

VASCULAR GRAFT RETRIEVAL AND EVALUATION

James M. Anderson, M.D., Ph.D., James Pelagalli, B.S. and Judie Frisch, R.N.

In an effort to monitor outcomes of common vascular operations which utilize graft materials, the implant retrieval and evaluation program at Case Western Reserve University, in collaboration with the Cleveland Vascular Society, has instituted a comprehensive program designed to determine morbidity and mortality modes and rates of graft failure. This program permits the analysis of data and materials provided by 29 surgeons located in 27 hospitals. Examination of the data base for 1979 shows that 927 reconstructions were carried out: 346 femoropopliteal, 240 aortofemoral, 81 femorofemoral, 44 axillofemoral and 216 aortoiliac procedures. The principal materials utilized in these procedures were Dacron (woven) 249, Goretex 232, Dacron (velour) 158, and autologous vein 152. The remainder were composites and other materials. The major complication was thrombosis of the graft usually resulting in thromboembolectomy during the same admission.

In addition to the data base provided through the computer registry of the Cleveland Vascular Society, the retrieval portion of the program permits the analysis of human vascular grafts in regard to their respective healing phenomena and blood-material interactions. This basic science component of our program is directed toward developing an understanding of the blood-material interactions and an appreciation of the factors controlling endothelial and pseudointima development in human vascular grafts.

Future Research Opportunities

In spite of the clinical success of vascular grafts, numerous questions regarding those interrelated in vivo factors which control success/failure remain unanswered. An animal model must be developed with appropriate consideration of the hemodynamics and blood-material interactions as they relate to the human. Further investigations into the question of endothelialization, pseudointima development, and the blood-material interactions of human vascular grafts must be carried out.

ANIMAL MODELS FOR THE EVALUATION OF VASCULAR GRAFTS

James A. DeWeese, M.D.

Much can be learned about vascular grafts without implanting them in animals. Tensile strength, elasticity, porosity, flow disturbances, and physical surface characteristics can be defined or measured. Thrombogenicity can be estimated by perfusion of grafts with blood components. Ultimately, however, the complete testing of any new graft material requires an in vivo experiment to evaluate the reaction of the graft to the host and of the host to the graft. Tensile strength may decrease and aneurysms occur, elasticity may be lost with fibrous ingrowth, kinking across flexion creases may impede blood flow. A mismatch of mechanical properties may initiate anastomotic intimal hyperplasia, excessively porous grafts may cause false aneurysms or mutagenesis may occur.

There is some evidence that the species of animal selected for a model is important. Graft healing in the dog more closely mimics that of men than in the pig, calf or baboon. The thoracic or abdominal aorta have been suitable testing grounds for medium-sized grafts but the carotid, femoral or coronary arteries provide a more severe test for the comparison of the failure rates of different graft materials. The slowing of blood flow by external compression or implantation into the venous system can also amplify differences in graft patency rates. An end-to-side anastomosis mimics the type of graft technique most commonly used clinically. Because of the turbulence which occurs, it theoretically proves a more severe test for a graft material than an end-to-end anastomosis.

The use of small to medium-sized grafts to bypass the ligated femoral arteries of dogs has provided a practical and suitable animal model for the comparison of graft materials. The patency rates observed in this model are similar to those reported in longer-term clinical evaluations. The replacement of short segments of femoral vein or the bypass of the canine circumflex coronary artery with grafts has had limited use but are worthy of continued evaluation as a discriminatory model.

PROSPECTIVE TRIALS OF VASCULAR PROSTHESES

Victor M. Bernhard, M.D., John J. Bergan, M.D., Frank Veith, M.D.

The ultimate value of any vascular prostheses should be determined by comparison with other grafts in a prospective randomized trial. It is noteworthy that no graft in use today has been investigated in this manner. The deficiencies of anecdotal, retrospective, and nonrandomized comparisons have been well documented and reliance upon these sources merely delays acquisition of unbiased information. This problem is of major importance in selecting arterial substitutes for limb revascularizations between the knee and ankle, where autogenous saphenous vein, the acknowledged "gold" standard, is frequently not available or is required elsewhere and must compete with more recently developed materials on the basis of conflicting reports.

In October 1978, three vascular surgery centers embarked upon a prospective randomized protocol comparing PTFE with autogenous saphenous vein. The investigators agreed to enter all patients requiring femoral-popliteal and femoral-tibial bypass grafts into a study approved by the human research committees of their associated institutions and also to be under the serveillance of an unbiased outside observer. Criteria were established for preoperative evaluation, patient selection, perative technique, postoperative followup and statistical methods. Patients with satisfactory saphenous veins who required either femoral-popliteal or femoral-tibial bypass were randomized into PTFE or vein categories after registering their informed consent. Those without a suitable saphenous vein were placed in an obligatory PTFE group for separate comparison with the randomized patient groups.

As of March 31, 1981, 284 patient limbs had been entered and followed up to 30 months. Statistical analysis is incomplete, however, the following trends have appeared. No difference has been noted between randomized ASV (n=50) and PTFE (n=51) when the distal anastomosis was placed above the knee. However, obligatory PTFE grafts appear to have a slightly greater rate of late thrombosis. Below the knee randomized PTFE (n=45) demonstrated a higher incidence of thrombosis at 3 months than ASV (n=46). Patency curves remained parallel thereafter.

Further statistical analysis will be required to demonstrate whether there are significant differences between below knee femoral-popliteal and femoral-tibial grafts in order to determine the need and justification of further patient entry into these subgroups.

GUIDELINES FOR EVALUATING A VASCULAR PROSTHESIS

J.D. Mortensen, M.D.

An unsatisfactory result from implantation of a vascular prosthesis can result from errors in implantation technique, inappropriate selection and/or application of a prosthesis to the specific clinical problem at hand, uncontrolled pathophysiologic processes existing in the patient, and/or by deficiencies or inadequacies in the prosthesis which is implanted. This communication is focused only on the latter problem. Scientific data for this report come from a recently completed comprehensive problem identification study of the safety and performance of vascular replacements, sponsored by the Food and Drug Administration.

Approximately 40 different deficiencies or inadequacies of vascular prostheses have been documented as causes for unsatisfactory clinical manifestations. These problems (tabulated and presented) fall into three major groups: 1) physical and mechanical deficiencies, 2) problems with biocompatibility, and 3) insufficient durability. Adequate evaluation of a vascular graft would logically include some type of investigation of each of these performance parameters.

Objective evaluation of the identified significant performance parameters of a vascular prosthesis poses a number of problems, including: 1) development and general acceptance of standardized, practical, and relevant tests for performance parameters; 2) implementation of objective testing, utilization of standardized reporting protocols, and optimal distribution to users of the results of evaluative testing; 3) development of a satisfactory system for obtaining and evaluating prostheses explanted after clinical (human) implantation; and 4) establishment of a practical and meaningful registry of complications attributable to deficiencies in vascular prostheses.

Specific research efforts focused on solving these problems associated with evaluating performance of vascular prostheses could include: 1) development of a more appropriate and relevant animal model for testing the performance characteristics of small diameter (bypass type) vascular prostheses; 2) further elucidation of the role of compliance, porosity, neointimal formation, and anastomotic occlusive processes in influencing the outcome of clinical implantation of small diameter vascular prostheses; 3) development and evaluation of practical nonbiologic, clinically relevant predictive tests and accelerated biologic response tests for vascular prostheses; and 4) relevant evaluation of prostheses explanted after clinical (human) implantation.

VASCULAR GRAFT STANDARDS DEVELOPMENT

Creighton B. Wright, M.D.

This presentation is designed to give some of the reasons for development of vascular graft standards and the past history and evolution of the present draft standard and rationale documents. Some of the continuing problems with vascular grafts will be identified, and the inexactitudes of graft standardarization will be discussed.

Future Research Opportunities

The techniques for relating graft characteristics to subsequent clinical preformance are rudimentary; and a great deal of further research into biomaterial bloodstream interactions, thrombosis, intimal hyperplasia, as well as strength requirements should provide ample opportunity for a number of scientists.

In particular, the draft standard should not conflict with future research and development, particularly for small vessel prostheses.

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